REMARKS

I. Disposition Of Claims

By this amendment, Applicant has canceled all pending claims, that is, Claims 9-19, prior to further examination of this application, in order to protect claims decided by the European Patent Office to be allowable, and, thus, for reasons unrelated to patentability. The file wrapper of the corresponding European patent application is attached: (1) Exhibit 1 is EPO Communication dated 7 May 2002; (2) Exhibit 2 is our letter to EPO dated 16 March 2001; (3) Exhibit 3 is EPO Communication dated 18 Sept 2000; (4) Exhibit 4 is our letter to EPO dated 11 June 1998; (5) Exhibit 5 is EPO Communication dated 2 December 1997; and (6) Exhibit 6 is International Preliminary Examination Report dated 25 August 1995. This amendment adds Claims 20-29, which correspond to Claims 1-10 found to be allowable by the European Patent Office, per EPO Communication dated 7 May 2002, attached as Exhibit 1. Thus, Claims 20-29 are presented for examination. Support for the amendment is found throughout the specification, as set forth in the chart of our letter to EPO dated 16 March 2001, attached as Exhibit 2, filed in response to EPO Communication dated 18 Sept 2000, attached as Exhibit 3. No new matter is added. Reexamination and reconsideration of the application, as amended, are respectfully requested.

II. Discussion of Malley et al. (5,521,161) and Lori et al.

The Office Action rejected the former claims under 35 U.S.C. §112, first and second paragraphs, because the Office Action questioned the use of functional language and the ingredients "ddC" and "AZT" for use in combination with hydroxyurea (HU) or a similarly active compound. The pending claims exclude the ingredients "ddC" and "AZT" for the reasons given in our letter to EPO dated 11 June 1998, attached as Exhibit 4, filed in response to EPO Communication dated 2 December 1997, attached

as Exhibit 5, repeating and extending the objections in International Preliminary Examination Report dated 25 August 1995, attached as Exhibit 6. Please be advised that all art cited by the EPO is of record, except WO84/00888 and USP 4,927,843, considered cumulative but attached herewith as Supplemental Information Disclosure Statement (IDS).

The Office Action takes the position that the disclosure of Malley et al. (5,521,161) specifically excludes the combination of hydroxyurea and AZT as inactive against HIV in quiescent cells in culture. The Office Action argues against the post-filing date art of Balzarini et al., Pharmacol Ther 2000 Aug-Sep, 87(2-3):175-187, of record. The Office Action accuses Applicant of missing the key inconsistency revealed by comparing the Malley disclosure with the disclosure of the above-identified application (Lori et al.), namely, in the Malley disclosure, AZT and HU are not shown to have a synergistic effect in the prevention of viral propagation, whereas in the Lori disclosure a very strong inhibitory effect is observed. Malley uses an assay to detect viral production which starts with quiescent cells, while Lori uses an assay that relies on activated cells. The Office Action concludes that "[b]ased on the factual basis for the claims in Malley et al. '161 (PTO-892 ref E) and the subsequent findings of Vila et al. (PTO-892 ref. XB), it appears to the examiner that there is a valid correlation between *in vitro* and *in vivo* anti-HIV results in quiescent cell culture-based tests, BUT there is not such a correlation with *in vivo* results when *in vitro* tests are conducted with activated cells in culture ala Lori et al."

MPEP 2107.03 states: "The applicant does not have to prove that a correlation exists between a particular activity and an asserted therapeutic use of a compound as a matter of statistical certainty, nor does he or she have to provide actual evidence of success in treating humans where such a utility is asserted. Instead, as the courts have repeatedly held, all that is required is a reasonable correlation between the activity and the asserted use."

The applicant must respectfully disagree with the logic the Office has used to dismiss the correlation between the Lori assays and *in vivo* results. First, the Office Action's introduction of Vila et al., showing the positive *in vivo* results of treatment with a combination of ddI and HU, does not reflect negatively on the method of Lori, since the success of this treatment was predicted by the Lori assay as well as the Malley assay. Thus both assays are predictive of *in vivo* activity. Second, it is not logically sound to conclude, especially in the biological sciences, that because an assay can predict a desirable *in vivo* activity based on a "positive" *in vitro* result, the assay can also firmly predict the lack of activity when a "negative" result is obtained, especially when another assay is yielding an opposite result. Third, it is possible for treatments that have a strong effect in the Lori assay, but a minimal or undetectable effect in the Malley assay, to still have a desirable effect *in vivo*, as shown in the example of treatment with AZT alone. AZT, which has been clinically useful in controlling viral propagation, has only a marginal inhibitory effect in the Malley assay when used at a concentration of 5 μM (Malley '161 Figure 2), but at this same concentration, full inhibition is observed in the Lori assay (Lori 6,046,175 Figure 2). Thus the assaying of activated cells, as used by Lori, may actually identify useful inhibitory activities that may not be recognized by a researcher that only makes use of the Malley assay with quiescent cells. For these three reasons, a reasonable correlation between the activities identified in activated cells as used by Lori and *in vivo* activity is present, as confirmed by Vila et al.

The claims meet the written description and enablement requirements of 35 USC § 112, first paragraph, as well as the definiteness requirement of 35 USC § 112, second paragraph, per the post-filing date art of Balzarini et al., Pharmacol Ther 2000 Aug-Sep, 87(2-3):175-187, of record. The argument that the findings of Balzarini 2000 to the effect that FddaraA plus HU is an effective treatment regiment for HIV is not believed by the Examiner because the test used to support this conclusion is a) done *in vitro* and b) done in the presence of activated cells (Lori test regimen), not the Malley test regimen, cannot stand. Precisely because the test used to support this conclusion is the Lori *in*

vitro test regimen done in the presence of activated cells, Balzarini 2000 confirms Table 7 to the effect that FddaraA plus HU is an effective treatment regiment for HIV. As shown by Vila et al discussed above, a reasonable correlation between the activities identified in activated cells as used by Lori and *in vivo* activity is evident.

Moreover, Balzarini 2000 confirms that, in view of the combination of hydroxyurea (HU), a ribonucleotide reductase inhibitor, and 2',3'-dideoxyinosine (ddI), a nucleoside reverse transcriptase inhibitor (NRTI), following the disclosure in the Malley and Lori patents, it was obvious that this principle should be viable for the combination of other NRTIs (page 179, second column, first line of new paragraph). It was also obvious that any modality that would act as a ribonucleotide reductase inhibitor could substitute for HU (page 176, second column, last line before section 2). Balzarini 2000 is convincing unbiased-third party observations from the peer-reviewed literature. It shows that functional language is consistent with the requirements of 35 U.S.C. §112, first and second paragraphs.

III. Discussion of Double Patenting

The Office action rejected the former claims on the grounds of obviousness-type double patenting over claims of USP 6,046,175, 6,194,390, 5,521,161, 5,736,527, and 6,093,702. By this amendment, Applicant has canceled conflicting claims and/or maintained a clear line of demarcation between the applications. A terminal disclaimer will obviate any remaining double patenting rejection.

CONCLUSION

In view of the above, it is submitted that the claims are in condition for allowance. Reconsideration and withdrawal of all outstanding rejections are respectfully requested. Allowance of the claims at an early date is solicited. If any points remain that can be resolved by telephone, the Examiner is invited to contact the undersigned at the below-given telephone number.

Respectfully submitted,

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